Spinal cord volume loss: A marker of disease progression in multiple sclerosis

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Abstract: OBJECTIVE Cross-sectional studies have shown that spinal cord volume (SCV) loss is related to disease severity in multiple sclerosis (MS). However, long-term data are lacking. Our aim was to evaluate SCV loss as a biomarker of disease progression in comparison to other MRI measurements in a large cohort of patients with relapse-onset MS with 6-year follow-up. METHODS The upper cervical SCV, the total brain volume, and the brain T2 lesion volume were measured annually in 231 patients with MS (180 relapsing-remitting [RRMS] and 51 secondary progressive [SPMS]) over 6 years on 3-dimensional, T1-weighted, magnetization-prepared rapid-acquisition gradient echo images. Expanded Disability Status Scale (EDSS) score and relapses were recorded at every follow-up. RESULTS Patients with SPMS had lower baseline SCV (< 0.01) but no accelerated SCV loss compared to those with RRMS. Clinical relapses were found to predict SCV loss over time (< 0.05) in RRMS. Furthermore, SCV loss, but not total brain volume and T2 lesion volume, was a strong predictor of EDSS score worsening over time (< 0.05). The mean annual rate of SCV loss was the strongest MRI predictor for the mean annual EDSS score change of both RRMS and SPMS separately, while correlating stronger in SPMS. Every 1% increase of the annual SCV loss rate was associated with an extra 28% risk increase of disease progression in the following year in both groups. CONCLUSION SCV loss over time relates to the number of clinical relapses in RRMS, but overall does not differ between RRMS and SPMS. SCV proved to be a strong predictor of physical disability and disease progression, indicating that SCV may be a suitable marker for monitoring disease activity and severity.

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ARTICLE

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Abstract

Objective

Cross-sectional studies have shown that spinal cord volume (SCV) loss is related to disease severity in multiple sclerosis (MS). However, long-term data are lacking. Our aim was to evaluate SCV loss as a biomarker of disease progression in comparison to other MRI measurements in a large cohort of patients with relapse-onset MS with 6-year follow-up.

Methods

The upper cervical SCV, the total brain volume, and the brain T2 lesion volume were measured annually in 231 patients with MS (180 relapsing-remitting [RRMS] and 51 secondary progressive [SPMS]) over 6 years on 3-dimensional, T1-weighted, magnetization-prepared rapid-acquisition gradient echo images. Expanded Disability Status Scale (EDSS) score and relapses were recorded at every follow-up.

Results

Patients with SPMS had lower baseline SCV ($p < 0.01$) but no accelerated SCV loss compared to those with RRMS. Clinical relapses were found to predict SCV loss over time ($p < 0.05$) in RRMS. Furthermore, SCV loss, but not total brain volume and T2 lesion volume, was a strong predictor of EDSS score worsening over time ($p < 0.05$). The mean annual rate of SCV loss was the strongest MRI predictor for the mean annual EDSS score change of both RRMS and SPMS separately, while correlating stronger in SPMS. Every 1% increase of the annual SCV loss rate was associated with an extra 28% risk increase of disease progression in the following year in both groups.

Conclusion

SCV loss over time relates to the number of clinical relapses in RRMS, but overall does not differ between RRMS and SPMS. SCV proved to be a strong predictor of physical disability and disease progression, indicating that SCV may be a suitable marker for monitoring disease activity and severity.

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Glossary

EDSS = Expanded Disability Status Scale; **LMER** = linear mixed-effects regression; **MLR** = multiple linear regression; **MS** = multiple sclerosis; **RRMS** = relapsing-remitting multiple sclerosis; **SC** = spinal cord; **SCV** = spinal cord volume; **SPMS** = secondary progressive multiple sclerosis; **T2LV** = T2 lesion volume; **T25-FW** = Timed 25-Foot Walk; **TBV** = total brain volume.

Multiple sclerosis (MS) is an inflammatory disease of the brain and the spinal cord (SC) that leads to demyelination and neurodegeneration. Atrophy is considered to be the consequence of neurodegeneration in MS and can be measured in vivo using MRI as a reduction of central nervous tissue volume.[1–5]

SC abnormalities have been observed in up to 83% of patients with MS, with 60% occurring in the cervical region.[6–8] SC lesions are of diagnostic as well as prognostic importance in MS.[9] However, previous studies were inconsistent regarding the correlation between lesional SC abnormalities and MS-related disability.[1,6,10] In contrast, SC volume (SCV) or cross-sectional area measurements have indicated a stronger and more consistent relationship to disability in MS.[4,8,10–16] Indeed, SCV loss has been shown to be more extensive in progressive forms of the disease.[12,16,17] It mainly reflects a diffuse process, which seems at best weakly related to focal brain and SC MS lesions.[1,18]

Despite the interest raised by cross-sectional and short-term follow-up volumetric SC studies, there is a lack of larger-scale, longer-term longitudinal studies on SCV loss in MS. This is mainly because the SC is infrequently included in imaging protocols because of cost, time restrictions, and technical difficulties in acquiring high-quality MRIs and in quantifying SC metrics in a reliable and time-efficient way.[19,20] As a result, there is a knowledge gap on the dynamic changes of SC measures and their association with the patient's clinical picture over time.

We hypothesized that SCV loss could be strongly associated with clinical changes over time, contributing stronger to disease progression than brain MRI measurements. Our aim for this study was to evaluate SCV loss in a large cohort of patients with relapsing-onset MS, who have been followed over a period of 6 years with annual clinical and MRI examinations. Our goal was to evaluate SCV loss as a feasible biomarker in MS in comparison to brain MRI metrics and assess potential between-group differences in a fast, clinically easy, applicable fashion using high-resolution brain and not SC scans.

Methods

Study design and participants

Clinical and MRI data of patients with relapsing-remitting MS (RRMS) and secondary progressive MS (SPMS) in an ongoing large-scale cohort study[7] (240 patients with relapse-onset MS in total) at a single center (MS Center, University Hospital, Basel) were analyzed. Patients were followed over a maximum of 6 years (7 annual time points). The diagnosis of MS was made in accordance with international panel established criteria.[21] The local ethics committee approved the study.

Procedures

All patients underwent a standardized neurologic examination including the Expanded Disability Status Scale (EDSS; neurostatus.org) by trained and certified examiners and Timed 25-Foot Walk (T25-FW) test annually. Definite clinical disease progression was defined according to the following conventions: (1a) an increase of 1 point in the EDSS if the baseline EDSS score was ≤5.5 *or* (1b) an increase of 0.5 point in the EDSS if the baseline EDSS score was >5.5, *and* (2) no relapse in the last 12 months. The number of relapses during the 12 months prior to every follow-up was noted with every clinical evaluation, as well as their sum from baseline to each follow-up.

All MRI scans were performed on the same 1.5T Magnetom Avanto MR scanner (Siemens Medical Solutions, Erlangen, Germany). Morphologic analyses were performed on high-resolution, 3-dimensional, T1-weighted magnetization-prepared rapid-acquisition gradient echo brain MRI scans acquired in sagittal orientation (repetition time/inversion time/echo time = 2,080/1,100/3.0 milliseconds; α = 15°, 160 slices, resolution: 0.98 × 0.98 × 1 mm^3), covering the upper cervical SC.

SCV analysis was performed using an established semiautomatic software (CORDIAL), which allows a fast and reliable segmentation and volumetry of the SC with minimal user interaction.[22,23] The segmentation was performed over a 35-mm-long SC segment, starting 27 mm below the cisterna pontis, which corresponds approximately to the SCV between the foramen magnum and the C2-3 intervertebral disk (figure e-1, links.lww.com/WNL/A588). Segmentations were visually inspected for quality and excluded from further statistical analysis in case of segmentation errors.

Total brain volume (TBV) was computed for each patient from the T1-weighted images with the fully automated tool "Structural Image Evaluation, using Normalization, of Atrophy" for cross-sectional studies (SIENAX version 2.6).[24] The SIENAX volume-correction factor was used for normalizing the TBV regarding variations of head size. All analyses were performed on these corrected volumes.

All brain white matter lesions (T2LV) were segmented by trained expert observers according to the standard operating procedures used at the local institution for the analysis of clinical phase II and phase III trials as described before.[25]

Statistical analysis

The mean annual SCV loss rate, the mean annual TBV loss rate, and the mean rate of annual T2LV increase over 6 years were determined for every patient as the average of the annualized changes between all available time points. To approximate a normal distribution, logarithmic (EDSS) and inverse transformations (T25-FW) were performed. The annual EDSS and annual T25-FW changes were calculated based on the transformed scores. See appendix e-1 (links.lww.com/WNL/A587) (including figure e-2, links.lww.com/WNL/A588) for exact calculation formulas of mean annual rates and changes.

Comparisons of baseline demographic factors, clinical measurements, and number of follow-ups between subtypes were made using the Welch and Pearson χ^2 test with Yates continuity correction. Between-group differences regarding baseline MRI measures and annual rates were performed using analyses of covariance, while correcting for age, sex, and disease duration.

Hierarchical multiple linear regression (MLR) analyses were performed to investigate the associations between annual rates of MRI metrics and annual changes of clinical scores, in a backward stepwise fashion. Independent variables were entered blockwise keeping the following sequence: first demographics and clinical factors, then SCV, and finally brain metrics. Baseline MRI and clinical measures were always entered into the model as correction factors to the respective annual rates, irrespective of whether they reached levels of statistical significance. All other independent variables that did not reach levels of statistical significance were not included in the final model.

Linear mixed-effects regression (LMER) analyses were deployed to explore the longitudinal correlations between clinical and MRI measures in a forward stepwise fashion, using a "random intercept" and a "random slope" to allow for within-subject and between-subject variance. Each factor was tested both for its contribution to the fit's intercept as well as to the fit's slope. The fit's intercept corresponds to the average of the dependent variable, whereas the fit's slope to the change of the dependent variable over time. Again, independent variables were entered blockwise in the above-mentioned sequence (see MLR). All independent variables without statistical significance were excluded from the final model.

To evaluate the prediction capabilities of MRI on disease progression and time to disease progression, a Cox analysis in a backward stepwise fashion was performed. In patients showing disease progression, the annual rates were recalculated for the time period between baseline and time of progression. A 10-fold cross-validation was performed, and the corrected concordance probability index (C index) was assessed. The contribution of each factor in the final model was assessed using the proportion of χ^2.

All statistical analyses were performed using R version 3.2.3 (r-project.org/).

Data availability

Raw data were fully generated at the University Hospital Basel. They were not acquired as part of a clinical trial. Derived data, e.g., MRI metrics (SCV, whole brain volume, etc.), supporting the findings of this study are available from the corresponding author (K.P.) upon reasonable request. The data are not publicly available because of ethical restrictions.

Results

Of 1,180 available MRI datasets of 240 relapse-onset patients, 95 datasets (8%; including the complete MRI series of 9 patients) were excluded from further analysis because of segmentation errors or image artifacts. This resulted in analysis of a total of 231 patients with MS (180 RRMS and 51 SPMS), who were followed on average over 5.1 ± 1.99 years (figure e-3, links.lww.com/WNL/A588). Demographics and basic clinical characteristics are described in table 1. Corrected baseline MRI metrics, annual rates, and between-group comparisons are shown in table 2.

SCV changes

In a first series of statistical analyses, SCV and its change over time was evaluated regarding demographic, clinical, and brain MRI metrics using LMER. The analyses revealed that men had larger average volumes than women (men: B = 289, $p < 0.001$), and a significantly faster SCV loss over time (men: B = −6.24, $p < 0.01$). Age (B = 3.36, $p < 0.01$) and disease duration (B = −7.94, $p < 0.001$) correlated with the average SCV but not with the SCV loss over time. Moreover, TBV ($B = 6 \times 10^{-4}$, $p < 0.001$) and T2LV ($B = 2 \times 10^{-3}$, $p < 0.05$) correlated with the average SCV but not with the SCV loss over time. SPMS on average had lower SC volumes (SPMS: B = −175, $p < 0.01$) than RRMS but not an accelerated SCV loss over time. Overall, the full model accounted for 98.7% of SCV variance, while the fixed effects alone accounted for 32.7%.

The sum of clinical relapses in patients with RRMS was associated with SCV loss over time (B = −1.06, $p < 0.05$) but not with the average SCV. Disease duration (B = −9.58, $p < 0.001$) was associated with the average SCV but not with the SCV loss over time. Age did not correlate with the SCV. The final model accounted for 98.7% of SCV variance, while the fixed effects alone accounted for 22.3% of the SCV variance.

SCV changes and disability

In a second step, we were interested in whether measures of disability (EDSS and T25-FW) are associated with SCV and brain MRI metrics and their changes over time.

Table 1 Demographics and basic clinical characteristics of patients with multiple sclerosis

Characteristics	Overall	RRMS	SPMS	*p* Value
No. of patients	231	180	51	
Baseline age, y				<0.001
Mean ± SD	44.7 ± 11.2	41.5 ± 10.1	55.4 ± 7.6	
Range	19–67	19–65	38–67	
Sex, F/M	160/71	133/47	27/24	<0.01
Baseline disease duration, y				<0.001
Mean ± SD	13.1 ± 9.2	11.4 ± 8.4	19.1 ± 9.7	
Range	0–47	0–40	1–47	
Baseline EDSS score				<0.001
Median	3.0	2.5	4.5	
Range	0–7.5	0–7.5	1.5–7.5	
Baseline T25-FW *z* score				<0.001
Mean ± SD	0 ± 1	0.26 ± 0.86	−0.98 ± 0.90	
Range	−2.69 to 3.90	−2.69 to 3.90	−2.67 to 1.02	
No. of follow-ups				0.38
Mean ± SD	5.10 ± 1.99	5.16 ± 1.99	4.88 ± 2.00	
Range	1–7	1–7	1–7	

Abbreviations: EDSS = Expanded Disability Status Scale; RRMS = relapsing-remitting multiple sclerosis; SPMS = secondary progressive multiple sclerosis; T25-FW = Timed 25-Foot Walk.
Between-group comparisons were performed using the Welch 2-sample *t* test and Pearson χ^2 test with Yates continuity correction where appropriate.

Expanded disability status scale

In the LMER analyses, SCV was inversely associated with the average EDSS score ($B = -4 \times 10^{-4}$, $p < 0.001$) and the EDSS worsening over time ($B = 2.1 \times 10^{-5}$, $p < 0.05$). TBV and T2LV were also correlated with the average EDSS score ($B = -2.2 \times 10^{-7}$, $p < 0.05$; $B = 8.8 \times 10^{-6}$, $p < 0.001$, respectively) but not with the EDSS worsening over time. Finally, sex (men: $B = 0.13$, $p < 0.05$), age ($B = 5.6 \times 10^{-3}$, $p < 0.001$), disease duration ($B = 2.8 \times 10^{-3}$, $p < 0.01$), and disease subtype (SPMS: $B = 0.35$, $p < 0.001$) correlated with the average EDSS score, but not with the EDSS worsening over time. The final model accounted for 87.7% of EDSS variance, while the fixed effects alone accounted for 42.6%.

Separate MLR analyses were performed to specifically investigate the extent of correlation between EDSS score and SCV in each disease type. In RRMS, the annual SC rate was the only predictive MRI factor, while age and baseline EDSS score contributed significantly. The final model demonstrated a weak prediction of the annual EDSS change variance, with an adjusted R^2 of 19.2%. Similar to RRMS, the annual SC rate was the most important predicting factor for the annual EDSS change in SPMS, while again age and baseline EDSS score also contributed significantly. The final model demonstrated, however, a moderate prediction of the annual change in EDSS, with an adjusted R^2 of 53.8%. The models are described in detail in table 3.

Timed 25-foot walk test

In the LMER analyses, SCV as well as TBV were inversely associated with the average T25-FW test score ($B = 3.7 \times 10^{-5}$, $p < 0.001$; $B = 6.8 \times 10^{-8}$, $p < 0.01$, respectively) but not with its worsening over time. T2LV correlated with both, the average T25-FW test score ($B = -1.4 \times 10^{-6}$, $p < 0.01$) and its worsening over time ($B = -2.2 \times 10^{-7}$, $p < 0.05$). Age ($B = -1 \times 10^{-3}$, $p < 0.001$), disease duration ($B = -6.2 \times 10^{-4}$, $p < 0.001$), and disease subtype (SPMS: $B = -5.7 \times 10^{-2}$, $p < 0.001$), but not sex, correlated with the average T25-FW test score. Only sex (men: $B = -2.9 \times 10^{-3}$, $p < 0.01$) and disease type (SPMS: $B = -4.5 \times 10^{-3}$, $p < 0.05$) correlated with the T25-FW worsening over time. The final model accounted for 94.2%, while the fixed effects alone accounted for 40% of the T25-FW variance.

Separate MLR analyses were performed to specifically investigate the extent of correlation between the T25-FW and SCV in each disease type. In the RRMS group, the annual SC rate was the most important predicting factor,

Table 2 Adjusted MRI measures of patients with multiple sclerosis

MRI measure	Overall	RRMS	SPMS	*p* Value
Baseline SCV, mm³				<0.001
Mean ± SD	2,380 ± 167	2,416 ± 148	2,253 ± 170	
Range	1,883–2,724	2,121–2,724	1,883–2,499	
Annual SCV rate, %/y				0.24
Mean ± SD	−0.43 ± 0.20	−0.38 ± 0.17	−0.62 ± 0.17	
Range	−0.95 to 0.04	−0.73 to 0.04	−0.95 to (−0.31)	
Baseline TBV, cm³				<0.001
Mean ± SD	1,489 ± 52	1,498 ± 46	1,433 ± 40	
Range	1,340–1,595	1,355–1,595	1,340–1,543	
Annual TBV rate, %/y				0.41
Mean ± SD	−0.43 ± 0.12	−0.41 ± 0.11	−0.50 ± 0.13	
Range	−0.75 to −0.17	−0.69 to −0.17	−0.75 to 0.17	
Baseline T2LV, mm³				0.18
Mean ± SD	6,287 ± 1,720	5,959 ± 1,515	7,437 ± 1,910	
Range	2,647–12,340	2,647–10,250	7,437–12,340	
Annual T2LV rate, %/y				<0.05
Mean ± SD	3.48 ± 2.53	4.34 ± 1.95	0.41 ± 1.91	
Range	−4.86 to 8.07	−2.90 to 8.07	−4.86 to 4.61	

Abbreviations: RRMS = relapsing-remitting multiple sclerosis; SCV = spinal cord volume; SPMS = secondary progressive multiple sclerosis; T2LV = brain T2 lesion volume; TBV = total brain volume.
Baseline SCV, TBV, and T2LV were adjusted for age, disease duration, and sex. Annual SCV rate, annual TBV rate, and annual T2LV rate were adjusted for age, disease duration, sex, and baseline SCV/TBV/T2LV, respectively. Adjusted values and significance of difference between RRMS and SPMS were obtained through analysis of covariance.

while baseline TBV also contributed significantly. The final model demonstrated a weak prediction of the annual T25-FW change variance, with an adjusted R^2 of 13.9%. Regarding the annual T25-FW test changes in patients with SPMS, the annual SC rate was the most important predicting factor, while baseline SCV also contributed significantly. The final model demonstrated a moderate prediction of the annual change in the T25-FW, with an adjusted R^2 of 49.9%. The models are described in detail in table 3.

Prediction of disease progression

Last, the predictive capabilities of MRI metrics on disease progression and time to disease progression were evaluated. A Cox analysis showed that disease type, baseline EDSS score, annual rate of SCV loss, and baseline TBV were significant predictors of disease progression. The annual rate of SCV loss explained 34% of the final model's χ^2 and was the strongest MRI measure. Its hazard ratio was 0.72 (95% confidence interval: 0.61–0.84, $p < 0.001$). Every 1% increase of the annual rate of SCV loss was associated with an extra 28% risk increase to develop disease progression in the following year. The C index resulting from a 10-fold cross-validation of the cohort was 70%, showing a moderate predictive power of the model. Details are displayed in table 4.

Discussion

This study is the first longitudinal longer-term analysis of SCV loss in MS investigating the upper cervical SCV in a large cohort of patients with relapse-onset MS for up to 6 years of follow-up. The temporal profile of SC tissue loss is illustrated with its association to clinical changes and its potential to monitor the clinical course of the disease. For that purpose, we deployed a fast, clinically easy applicable pipeline using high-resolution brain scans.

The SC segmentation was performed in a mainly automatic fashion with minimal user interaction, thus avoiding bias from manual segmentations or manual corrections. Our approach using the upper cervical SCV instead of the upper SC area is thought to be less susceptible to possible bias from focal atrophy due to lesions and possesses high test-retest reliability.[22]

Table 3 Multivariate analysis of clinical measures by disease type

Group	Final model	Variable	β	*p* Value	ΔR^2
RRMS	Annual EDSS change ~ age + baseline EDSS + baseline SCV + annual SCV rate; adjusted R^2 = 19.19%; $p < 0.001$	Age	0.25	<0.001	17.38%, $p < 0.001$
		Sex	—	NS	
		Disease duration	—	NS	
		Baseline EDSS	−0.51	<0.001	
		Baseline SCV	−0.10	NS	
		Annual SCV rate	−0.16	<0.05	1.81%, $p < 0.05$
		Baseline TBV	—	NS	—
		Annual TBV rate	—	NS	—
		Baseline T2LV	—	NS	—
		Annual T2LV rate	—	NS	—
	Annual T25-FW change ~ baseline T25-FW + baseline SCV + annual SCV rate + baseline TBV; adjusted R^2 = 13.87%; $p < 0.001$	Age	—	NS	0.33%, $p = 0.23$
		Sex	—	NS	
		Disease duration	—	NS	
		Baseline T25-FW	−0.08	NS	
		Baseline SCV	0.07	NS	
		Annual SCV rate	0.35	<0.001	11.51%, $p < 0.001$
		Baseline TBV	0.18	<0.05	2.03%, $p < 0.05$
		Annual TBV rate	—	NS	—
		Baseline T2LV	—	NS	—
		Annual T2LV rate	—	NS	—
SPMS	Annual EDSS change ~ age + baseline EDSS + baseline SCV + annual SCV rate; adjusted R^2 = 53.83%; $p < 0.001$	Age	−0.27	<0.05	18.25%, $p < 0.001$
		Sex	—	NS	
		Disease duration	—	NS	
		Baseline EDSS	−0.23	<0.05	
		Baseline SCV	0.03	NS	
		Annual SCV rate	−0.60	<0.001	35.58%, $p < 0.001$
		Baseline TBV	—	—	—
		Annual TBV rate	—	—	—
		Baseline T2LV	—	—	—
		Annual T2LV rate	—	—	—
	Annual T25-FW change ~ baseline T25-FW + baseline SCV + annual SCV rate; adjusted R^2 = 49.89%; $p < 0.001$	Age	—	NS	8.38%, $p < 0.01$
		Sex	—	NS	
		Disease duration	—	NS	
		Baseline T25-FW	0.06	NS	

Continued

Table 3 Multivariate analysis of clinical measures by disease type *(continued)*

Group	Final model	Variable	β	*p* Value	ΔR^2
		Baseline SCV	−0.26	<0.05	
		Annual SCV rate	0.65	<0.001	41.51%, $p < 0.001$
		Baseline TBV	—	NS	—
		Annual TBV rate	—	NS	—
		Baseline T2LV	—	NS	—
		Annual T2LV rate	—	NS	—

Abbreviations: β = standardized regression coefficients; ΔR^2 = adjusted R^2 difference; EDSS = Expanded Disability Status Scale; NS = not significant; RRMS = relapsing-remitting multiple sclerosis; SCV = spinal cord volume; SPMS = secondary progressive multiple sclerosis; T2LV = brain T2 lesion volume; T25-FW = Timed 25-Foot Walk; TBV = total brain volume.

In line with previous cross-sectional studies,[4,5,10–17] patients with SPMS had lower SCV compared to patients with RRMS. However, there was no evidence of accelerated SCV loss over time in SPMS compared with RRMS. The observed between-group differences in cross-sectional settings can be explained by longer disease duration and older age of the patients with SPMS (figure 1), arguing against a theoretical preferential SCV loss in this group as suggested by previous smaller-scale and shorter-duration studies.[4,5,10–17] Similar findings were present regarding TBV loss when compared between groups in the present cohort. This is in line with a large study by De Stefano et al.[3] showing that there is no difference in the rate of brain volume loss in earlier vs more advanced MS phenotypes on a group level. Overall, these results indicate that the rate of tissue loss in the CNS is in general comparable in relapse-onset MS phenotypes.

In terms of T2LV, patients with RRMS showed faster accumulation of T2LV, reflecting the inflammatory activity dominating in this phase of the disease. However, SCV loss over time seemed to be largely independent of change in TBV and T2LV.

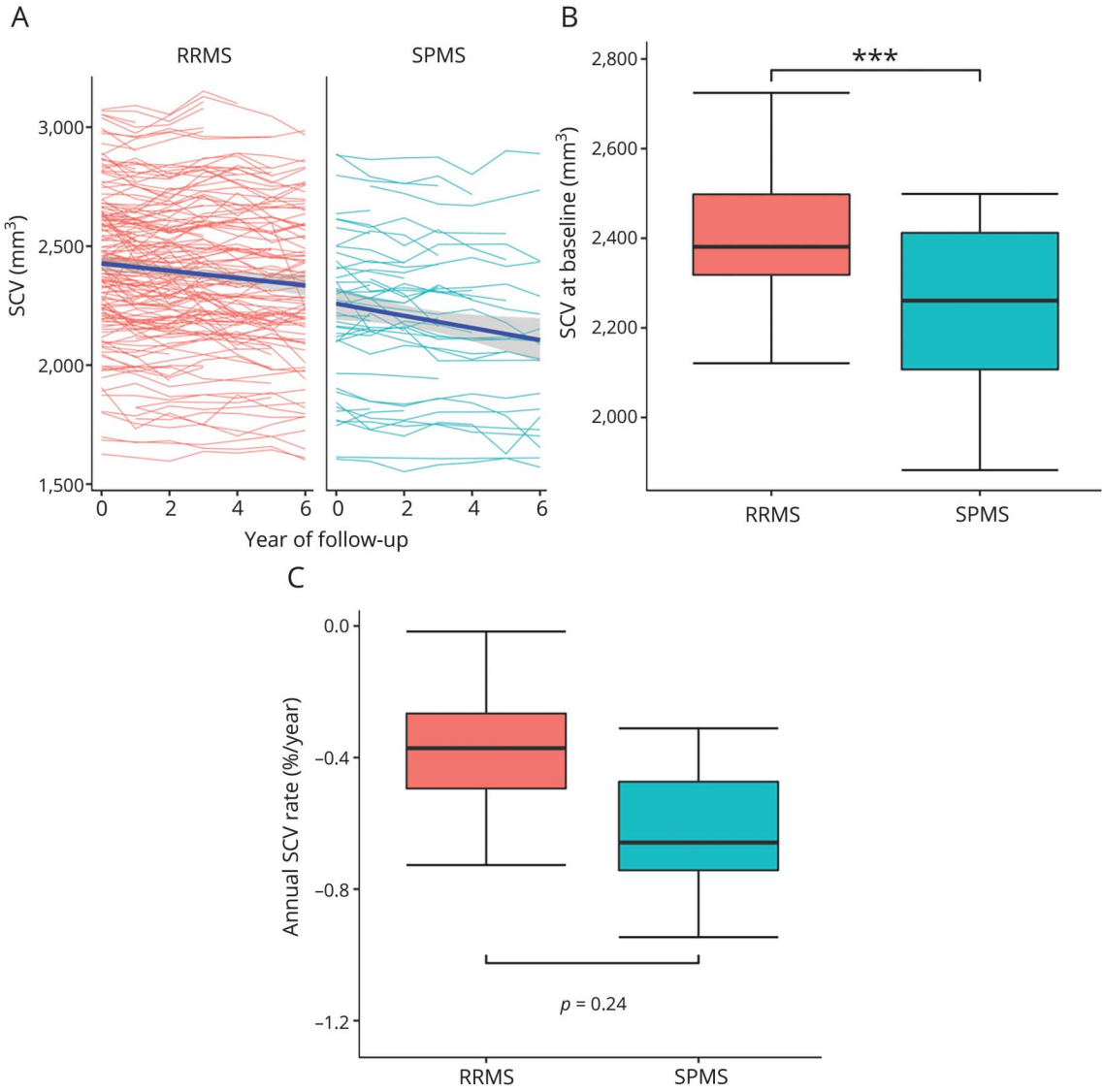
As expected, men had larger SCV at baseline; however, they exhibited more pronounced SCV loss over time, which is in line with the clinical observation that male sex is an indicator

Table 4 Cox analysis of disease progression

Final model	Variable	HR (95% CI)	Proportion of χ^2, %	*p* Value
(Disease progression, time to disease progression) ~ disease type + baseline EDSS + baseline SCV + annual SCV rate + baseline TBV	Age	—	—	NS
	Sex	—	—	NS
	Disease duration	—	—	NS
	Disease type (SPMS)	4.62 (2.46–8.67)	43.9	<0.001
	Baseline EDSS	0.29 (0.15–0.58)	24.3	<0.001
	Baseline SCV	1.0008 (1.0–1.002)	6.7	NS
	Annual SCV rate	0.72 (0.61–0.84)	34	<0.001
	Baseline TBV	1.0000 (1.0000–1.0000)	18	<0.01
	Annual TBV rate	—	—	NS
	Baseline T2LV	—	—	NS
	Annual T2LV	—	—	NS

Abbreviations: CI = confidence interval; C index = 10-fold cross-validation corrected concordance probability index; EDSS = Expanded Disability Status Scale; HR = hazard ratio; NS = not significant; SCV = spinal cord volume; SPMS = secondary progressive multiple sclerosis; T2LV = brain T2 lesion volume; TBV = total brain volume.
Concordance = 0.717 (SE = 0.04); Wald test = 51.53, $p < 0.001$; score (log-rank) test = 54.16, $p < 0.001$; total $\chi^2 = 51.54$, $p < 0.001$; C index = 0.70.

Figure 1 SCV and its change over time separated by disease type: patients with RRMS (red) and SPMS (turquoise)



(A) The fine lines represent the raw measurements of SCV for each patient over 6 years of follow-up, while the thicker blue lines depict the respective "trends" of SCV loss in the 2 disease types. Of note, despite a significant difference of SCV at baseline (B), the annual SCV rate did not differ significantly between disease types, after adjusting for age, sex, and disease duration (C). The error bars (whiskers) represent the mean ± SD. RRMS = relapsing-remitting multiple sclerosis; SCV = spinal cord volume; SPMS = secondary progressive multiple sclerosis.

of poorer prognosis.[26] Yet, our statistical analyses predicting the EDSS and disease progression could not confirm a faster clinical worsening of male patients compared to females. This may be explained by the follow-up span, which might not have been long enough. Neither age nor disease duration seemed to have an effect on SCV loss over time, suggesting a relatively steady SC tissue loss in both patient groups.

In RRMS, an increased cumulative number of clinical relapses was associated with faster SCV loss over time. One may speculate that with every new clinical relapse in a patient with RRMS, some degenerative cascade is activated accelerating SCV loss, an effect that seems to persist way beyond the initial acute inflammatory phase of the relapse. The data further suggest that the accumulation of clinical relapses shapes—at least partially—a patient's profile in terms of SCV loss. The data also imply that the reduction of clinical relapses, which constitutes a fundamental therapeutic strategy of RRMS, should beneficially affect this process.[27] In the LMER, SCV proved to be the only MRI metric to strongly explain the clinical progression over time as measured by speed of EDSS worsening for the whole cohort. TBV and T2LV were associated with the average patient's disability but did not independently relate to EDSS worsening over time, when added to a statistical model that included SCV. Regarding the T25-FW test, SCV and TBV correlated with the patient's walking speed, although they failed to correlate with its worsening over time. Instead, the T2LV was a predictor of these changes, probably driven by the RRMS group.

Regardless of a similar SCV loss pace in both patient groups, association of the annual rate of SCV loss with clinical scores was remarkably higher for patients with SPMS than for the RRMS group in all analyses. This shows that despite the assumption of the same underlying causal pathomechanisms,[27,28] the clinical effect in SPMS is more pronounced. This can be explained by older age and accumulation of damage over time in patients with SPMS, entailing chronic immune activation, increased oxidative stress–related damage, loss of trophic support, and exhaustion of repair and compensatory mechanisms.[28,29] This allows axonal and myelin damage to be "translated" in a much more straightforward way into clinical deficits once the threshold of neuronal injury and/or repair has been exceeded. However, it is possible to hypothesize that patients with RRMS still have sufficient reserves of cortical adaptation, remyelination, axonal repair, and neuroprotection, which allow them on one hand to maintain or reestablish the functionality of neuronal tissue and on the other hand "mask" the produced axonal loss through neuroplasticity occurring at higher cortical centers.[1,21,22] Considering that, in future works, additional measures of neuroprotective mechanisms such as quantitative MRI measurements (e.g., magnetization transfer imaging, diffusion tensor imaging, and proton magnetic resonance spectroscopy) may shed light into this interesting aspect of the disease.[28,30,31] The annual SCV loss rate was to a great extent the only MRI factor in predicting clinical worsening, while the annual TBV and T2LV did not significantly contribute. Predicting disease progression using a Cox analysis, it was shown that the annual rate of SCV loss was the strongest MRI measure, and a 1% rate increase was associated with a 28% risk increase to develop disease progression in the following year. Furthermore, patients with SPMS were shown to be more susceptible to disease progression. This also adds to evidence that SCV could possibly be a better disease marker compared to brain volume loss and lesion load in the brain.

This study has a number of limitations. We aimed to analyze follow-up data of a group of patients with MS in a retrospective manner. Some patients were lost to follow-up during the study, leading to incomplete datasets and potential bias. While the group of patients with SPMS was smaller than the RRMS group, the 2 groups were followed up for a similar amount of time. The latter at least does not support a preferential loss of patients with progression. Furthermore, the lack of a representative control group of healthy subjects made it impossible to assess MS-related SC volume loss as compared to SCV decline due to normal aging. However, it is likely that the observed SCV loss is mainly a disease-related effect because in the normal population, the degree of SCV loss seems to be smaller.[32] Unfortunately, no study has so far assessed the effect of age on SCV loss in healthy controls longitudinally. In this study, the potential effect of disease-modifying drugs on inflammation, and ultimately on SCV variation, was not included in our analysis. In our cohort, 68% of patients were treated with disease-modifying drugs at baseline including primarily first-line injectables (63%). While injectables also show an effect on brain atrophy, we believe that this effect is rather negligible.[33] Finally, since the study had no T2-weighted sequence covering the area of volume measurement over all time points analyzed here, the impact of SC lesions was not assessed.

In conclusion, this study indicates that measurement of SCV loss represents a reliable imaging marker for monitoring disease activity and progression in MS. SCV loss was shown to be directly affected by inflammatory events (relapses), supporting at least a partial role of inflammation in driving neurodegeneration in MS. Finally, the study provides evidence of a dissociation in the clinical consequences of SC volume loss in RRMS vs SPMS. That said, SCV could be a useful endpoint in clinical trials of therapeutic agents aimed at the degenerative process in MS, a much wanted, unmet need.

Author contributions

C.T.: study concept and design, image analysis, statistical analysis and interpretation of the data, draft, revision and final approval of manuscript. S.M.: study concept and design, statistical analysis and interpretation of the data, revision and final approval of manuscript. L.G.: image analysis, statistical analysis, final approval of manuscript. S.P.: methods development and data analysis, final approval of manuscript. Y.N.: acquisition of clinical data, final approval of manuscript. M.A.: acquisition of data, image analysis, final approval of manuscript. C.S.: final approval of manuscript. P.C.: methods development and data analysis, final approval of manuscript. O.B.: final approval of manuscript. J.W.: final approval of manuscript. T.S.: study concept and design, interpretation of the data, draft, revision and final approval of manuscript. L.K.: study concept and design, acquisition of clinical data, interpretation of the data, revision and final approval of manuscript. K.P.: study concept and design, acquisition of clinical data, image analysis, statistical analysis and interpretation of the data, draft, revision and final approval of manuscript.

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Spinal cord volume loss: A marker of disease progression in multiple sclerosis

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